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MONICA/ECTIM Meeting Report: Heart attacks in France and Northern Ireland.

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INTRODUCTION

The MONICA centres in Belfast, Lille, Strasbourg and Toulouse have taken part in the WHO coordinated MONICA (MONItoring in CArdiovascular diseases) Project since the early 1980s. In order to test the Project's main objective to investigate the relationships between 10 year trends in the major CVD risk factors (serum cholesterol, blood pressure and cigarette consumption) and 10 year trends in incidence rates, the centres register coronary events and carry out risk factor surveys. The registration of events validates a four-fold greater incidence of ischaemic heart disease in Belfast than Toulouse, and the risk factor surveys show that the major risk factors are identical between these two centres. A dietary comparison also shows no important differences apart from a higher polyunsaturated fat, wine, cheese, fruit and vegetable intake in Toulouse (See Abstract 3).

Since 1988 a programme of studies has been mounted in the four centres. A large case-control study (ECTIM) completed its intake of 1,474 cases and controls in 1992 (See Abstract 4). In Belfast the ECTIM Study has been extended to women and into the families of the probands. PRIME, a cohort study began recruitment in 1991 (See Abstract 22). This recruitment will be concluded in the autumn of 1993 with a total intake of 11,000 middle-aged males in Northern Ireland and France; thereafter, there will be a 5 - 7 year follow-up. Intervention studies are also planned within this research programme.

This major collaboration, in addition to the four MONICA centres, involves several laboratories in Northern Ireland and France.

The two day meeting at Queen's University, held in conjunction with the Irish Hyperlipidaemia Association, was attended by 50 visitors from France, Switzerland, Spain, Scotland, England, Wales and the south of Ireland. It was opened by Dr Ivan Gyarfas, Chief of Cardiovascular Disease in WHO, Geneva. Key items presented and discussed were the deletion polymorphism of the ACE gene which has been identified as a risk factor for myocardial infarction in the ECTIM Study (See Abstract 9 and 19); the HVR48+ polymorphism of the apolipoprotein B gene which carries a high odds ratio for myocardial infarction in overweight subjects in Belfast and France (See Abstract 12); and polymorphisms of the lipoprotein lipase gene (See Abstract 15) which also appears to predispose to myocardial infarction. The major lipid difference between the French and Northern Irish populations is a lipid profile characterised by high levels of LpE:B and Lp(a)B and low levels of LpA1 in Belfast (See Abstract 7).

In conclusion, the contribution of molecular genetics to traditional epidemiology is immense as we are beginning to understand how environmental risk factors interact with the individual's genetic constitution.

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HEART ATTACKS IN NORTHERN IRELAND

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The Belfast MONICA Project has been registering coronary heart disease events as part of the WHO coordinated Project since 1983. The area covered is to the east of the Province (Belfast, Castlereagh, North Down and Ards Health Districts) with a total population of 510,000 persons. Despite its pre-eminence in ischaemic heart disease mortality during the 1980s when it vied with Scotland for the premier position in age-standardised rates for both men and women (40-69 years), over the decade 1980-90 statutory age-standardised IHD mortality data showed a 30% decline in men and a 25% decline in women (40-69 years). MONICA event registration data for males aged 25-64 years in Belfast showed a peak in 1984 of 431/100,000, with a decline to 272/100,000 in 1990: the corresponding rates in females were 137 and 100/100,000. Population surveys took place in 1983-4, 1986-7 and 1991-2 and risk factor data were assembled. Applying two multiple logistic function scoring systems (UK Heart Disease Prevention Project - age, cigs, chol, systolic BP and BMI and the British Regional Heart Study - age, cigs, chol, HDL-chol, mean BP and BMI), which estimate the chance of developing heart disease over the subsequent 4-5 years, resulted in trends which were broadly in agreement with the trends in incidence.

HEART ATTACKS IN FRANCE: CORONARY MORTALITY AND MORBIDITY, GEOGRAPHIC AND TEMPORAL TRENDS (1985-89)

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The three French MONICA centres are located in the areas of Toulouse (TOU), Strasbourg (STRA) and Lille (LIL), respectively in the south, east and north of the country. They cover similar sample size populations (about 500,000 inhabitants, aged 35-64 years). Acute coronary events are monitored and classified following the MONICA protocol but taking also into account medical diagnoses or death certification. There were 11,310 coronary acute events (ALL) with 57,331 definite acute myocardial infarctions (AMI) and 3,004 coronary deaths (CD) for the period 1985-89. Male cases made up 81% of ALL.

The first table gives age-standardized mean annual rates per 1000 for AMI, ALL and CD. Except for AMI, rates are slightly lower in TOU, particularly in females.

	MALES				FEMALES			
	TOU	STR	LIL	p	TOU	STR	LIL	p
AMI	1.82	2.13	1.73	≤0.001	0.22	0.43	0.28	≤0.001
ALL	3.53	4.10	3.91	≤0.001	0.56	0.98	0.85	≤0.001
CD	0.77	1.13	1.16	≤0.001	0.13	0.26	0.22	≤0.001

The second table gives age-standardized trends estimated from a logistic regression model and expressed as a relative percentage variation of rates during the period (men only).

	TOU	p	STR	p	LIL	p
AMI	–4	ns	–13	≤0.05	–25	≤0.001
ALL	+6	ns	–6	ns	–18	≤0.001
CD	–32	≤0.001	–21	≤0.02	–19	≤0.05

In general, all rates are decreasing in LIL, but attack rates for all events are stable in TOU and STR. CD are strongly decreasing in all centres in agreement with official death statistics. Coronary morbidity and mortality are not homogeneous in France. Such a geographic and temporal variability merits discussion and further research.

PREVIOUS NUTRITIONAL STUDIES

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Several hypotheses have been put forward to explain the differences in the incidence of CHD and mortality between France and North European countries. The incidence is fourfold higher in Belfast than in the 3 French registers. Conventional cardiovascular risk factors do not account for such differences. Population surveys carried out within the framework of MONICA registers and the ECTIM study reflect the absence of striking differences in conventional risk factors between France and Northern Ireland. Specific regional nutritional habits might account for the differences in the frequency of disease. The Belfast MONICA Centre and the 3 French registers participated in a nutritional survey (EURONUT) carried out in a representative population sample. The comparative analysis of the results of the initial nutritional survey, which was carried out in men aged 45-64 years in Belfast and in Toulouse, shows a higher consumption of polyunsaturated fatty-acids in the Haute-Garonne (7.1% vs 4.6% of total energy) with a higher P/S ratio (0.50 vs 0.30), a lower alcohol consumption in Belfast (3.6% vs 6.4% of total energy) and a higher intake of fruit and vegetables in the Haute-Garonne. The vitamin C serum level found in males is twofold higher in Haute-Garonne (Gey et al 1991) in accordance with the amount of vegetable intake. Nutritional behaviour differences seem to corroborate the hypothesis of the protective role of unsaturated fat and vitamins (E and C) against IHD. The predictive aspect of the different risk factors (lipoprotein profile, antioxidants) highlighted by the MONICA population surveys must be investigated in the framework of a prospective study (PRIME Study) now being carried out in Belfast and in the 3 French MONICA Centres.

GENERAL DESIGN OF THE ECTIM STUDY

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The ECTIM Study is a multicentre case-control study set up to investigate the large differences in ischaemic heart disease incidence and mortality between centres taking part in the WHO MONICA Project: the three French Centres (Strasbourg, Toulouse, Lille) and the Northern Ireland Centre in Belfast. The aim of the study is to compare the frequency of DNA polymorphisms in patients having suffered an acute myocardial infarction (MI) and in controls, and to study the association between these polymorphisms and various factors involved in the metabolism of lipids and of clotting factors: 662 cases and 812 controls were included between December 1988 and May 1992.

The cases and controls were men aged 25-64 years resident in the geographical areas covered by the MONICA registers. Their family had to have settled in the region for at least 2 generations. The cases were patients with a definite acute MI (MONICA Diagnostic Category 1), surviving 3 to 9 months after the acute event. The controls were age-matched men from the same population as the cases. The participation rates were 60% in Belfast, 68% in Toulouse, 56% in Strasbourg and 55% in Lille.

The cases and the controls were interviewed in a standardised way in the four centres, mostly by home visiting. The questionnaire for cases and controls concerned personal and familial histories as well as exposure to potential deleterious factors for the cardiovascular system (smoking habits, alcohol consumption, blood pressure measurement, anthropometric measurements etc). Furthermore, there was a specific questionnaire for controls, based on the ROSE questionnaire, and another for cases which collected clinical data concerning the acute event.

A blood sample was taken on fasting subjects for the setting up of a DNA bank, a plasma bank, the measurement of lipid parameters and clotting factors. The biological measurements were all centralised in specialised laboratories.

MEDICAL TREATMENT AFTER MYOCARDIAL INFARCTION: THE ECTIM STUDY

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The prescriptions six months after a myocardial infarction were compared between the different centres of the ECTIM Study (662 Patients). French patients took significantly more medicine than Northern Irish (4.65±1.57 vs 4.17±1.57 respectively, $p<0.001$). French patients had a higher frequency of hypolipidaemics, oral anticoagulants and ACE inhibitors (35% vs 5.5%, $p<0.001$; 23% vs 1.5%, $p<0.001$ and 18% vs 5%, $p<0.001$, respectively), while the Northern Irish had a higher frequency of beta-blockers and antiaggregating drugs (67% vs 54%, $p<0.01$ and 88% vs 67%, $p<0.001$, respectively). Three-quarters of the patients took anti-angina drugs (nitrates and non-nitrates), but the Northern Irish patients were almost exclusively on nitrates, while the French patients' nitrate and non-nitrate intakes were similar.

In France, a north-to-south gradient of the number of medicines prescribed was found (5.04±1.59 in Lille, 4.74±1.50 in Strasbourg and 4.27±1.57 in Toulouse, $p<0.001$). The frequency of the prescriptions of oral anticoagulants (38%, 5% and 15%, $p<0.001$), hypokalaemic diuretics (17%, 8% and 8%, $p<0.01$), and antiaggregating drugs (55%, 89% and 63%, $p<0.001$) were also different between Strasbourg, Lille and Toulouse, respectively.

In conclusion, there is a lack of consensus as regards the therapy after a myocardial infarction. A follow-up study is currently under way to assess the outcome of the patients from each ECTIM centre.

CARDIOVASCULAR RISK FACTORS IN THE ECTIM STUDY

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The aim of this study is to compare patients with myocardial infarction (category 1 MONICA) and controls. Cases and controls were born in the area of the four MONICA centres (Belfast, Lille, Strasbourg and Toulouse).

	FRANCE			BELFAST		
	Cases (n=460)	Controls (n=609)		Cases (n=202)	Controls (N=202)	
Previous history (%)			OR*			OR
- Diabetes	13.7	7.4	1.9	6.4	3.0	2.2
- High blood pressure	33.0	19.7	2.1	17.3	14.3	1.3
- Hyperlipidaemia	37.3	21.1	2.4	11.4	4.4	3.2
Tobacco						
- Number of cigs	8.6	5.7	p<0.001	15.9	5.1	p<0.001
-Smokers(%)	41.5	31.0	p<0.001	55.9	25.2	p<0.001
Alcohol (ml/day)						
- Wine	23.9	29.5	p<0.05	0.5	1.7	p<0.05
- Beer	6.9	8.6	NS	16.4	18.2	NS
- Spirits	2.0	3.7	p<0.001	17.2	17.1	NS
- Total Alcohol	32.0	41.0	p<0.001	34.2	37.2	NS

* OR = Odds ratio

This study confirms the role of the four risk factors in the incidence of myocardial infarction. Alcohol and alcohol type also seems to play a part. The part that alcohol plays in protection from atherosclerosis is clearly different in France than in Belfast.

LIPID AND LIPOPROTEIN PARAMETERS IN THE ECTIM STUDY

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The incidence of coronary heart disease (CHD) in middle-aged men is more prevalent in Northern Ireland than in France. The ECTIM Study was undertaken to investigate the differences in CHD incidence and mortality between the French populations of Strasbourg, Toulouse and Lille and the Northern Irish people in Belfast. In the present study, an investigation of lipid parameters was performed in normocholesterolaemic patients with myocardial infarction and controls, with a particular emphasis on lipoprotein particles defined by their apolipoprotein composition.

In Belfast and France, cases had lower levels of HDL-cholesterol, Apo A-I, Apo A-II, LpA-I and LpA:AI and higher levels of LpE:B and Lp(a):B than controls. Triglycerides, VLDL-cholesterol, Apo B and LpCIII:B were higher in cases than in controls only in Belfast. In controls, the levels of cholesterol fractions and apolipoproteins were similar in the two countries; however, the level of LpA-I was lower and the levels of LpE:B and Lp(a):B were higher in Belfast than in France.

A high-risk profile, characterized by a low LpAI level and by high levels of LpE:B and Lp(a):B, was thus more frequent in the population of Northern Ireland.

The data indicate that measurement of lipoprotein particles defined by their apolipoprotein composition may be useful indicators of CHD risk. However, this profile must be assessed in prospective studies to estimate its predictive value.

THROMBOTIC FACTORS IN THE ECTIM STUDY: A MINI-REVIEW

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Plasma levels of fibrinogen, factor VII coagulant activity (fVIIc) and plasminogen activator inhibitor type-1 (PAI-1) were measured on participants in the ECTIM study. Mean plasma fibrinogen levels were consistently and markedly higher in cases than in controls, even after adjustment for smoking and other confounding factors. There was significant variation in mean fibrinogen levels between centres in the controls, with Belfast being highest (314 mg/dl) and Toulouse lowest (291 mg/dl), with Lille and Strasbourg (both 305 mg/dl) intermediate. This geographical variation may go some way towards explaining the differences in incidence of coronary heart disease (CHD) between Northern Ireland and France. Mean fVIIc was, in all centres, higher in controls than in cases, which does not support previous observations from prospective studies, although different fVIIc assays have been used in different studies. In all regions except for Belfast, PAI-1 levels were higher in controls than in patients, raising questions as to the role of PAI-1 in CHD. Among the controls, PAI-1 levels were significantly higher in the French centres than in Belfast, an unexpected and currently inexplicable finding. In conclusion, the results of the ECTIM study strengthen the epidemiological evidence for a possible role for fibrinogen in the pathogenesis of CHD but do not confirm previous studies which implicated plasma fVIIc and PAI-1 levels as risk factors for CHD.

PARENTAL HISTORY OF MYOCARDIAL INFARCTION IN FRANCE AND NORTHERN IRELAND

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The objectives of the present study were to compare the prevalence of parental history of coronary heart disease and its impact on individual risk of myocardial infarction (MI) in Northern Ireland and France, and to identify which factors could partly explain the familial concentration of disease. Parental history was investigated at interview by specially trained staff. In Belfast, data were validated from General Practitioner or hospital records or death certificates, and those for whom this validation was not possible (15%) were excluded. In France, confidentiality legislation does not permit such validation, and self-reported history was used. Positive parental history was more frequent in Northern Ireland than in France (24% vs 10% in controls' fathers, 14% vs 3% in controls' mothers). In both countries, prevalence of MI was higher, and mean age of onset was lower, in cases' than in controls' parents. The odds ratios for disease associated with a premature parental MI (≤60 yrs for fathers/≤65 yrs for mothers) were 2.3 ($p<0.001$) in France and 2.8 ($p<0.01$) in Northern Ireland respectively, whereas those associated with a late parental MI were 2.0 ($p<0.001$) and 1.4 ($p=0.09$), respectively.

In the control populations, lipid and lipoprotein levels were compared between individuals with and without parental history. LpAI, ApoAII, triglyceride and Lp(a) levels did not differ between the two groups, whereas total cholesterol and ApoB levels were significantly raised among those with a positive parental history. The difference was even more marked when the parental history was restricted to premature MI (ApoB level: 1.44 vs 1.30; $p<0.01$). Comparison of genetic polymorphisms between the two groups indicated a higher frequency of ApoE (44+43) phenotypes among those with premature history (OR=2.4; $p=0.02$). There was also an excess of angiotensin-converting enzyme DD and ID genotypes among those having a parental history, which was even more marked when parental history was restricted to fatal MI (OR=2.8, $p<0.01$ for DD; OR=2.0, $p=0.06$ for ID).

HOW RELIABLE IS A FAMILY HISTORY OF MYOCARDIAL INFARCTION?

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Previous studies have shown that a positive family history of myocardial infarction (MI) contributes significantly and independently to individual risk. Less frequently has the reliability of self-reported family histories been assessed. Our objective was to assess the reliability of reports of MI in first degree relatives of Belfast ECTIM recruits.

Of the original 400 cases and controls in Belfast, 349 were interviewed approximately 18 months to 2 years after their initial recruitment. Demographic and clinical histories were obtained in respect of 2812 first degree relatives. Death certificates were retrieved for 753 of 783 deceased relatives. The medical history of 93% of living first degree relatives (1893/2029) was verified primarily through correspondence with family doctors and retrieval of hospital records.

The sensitivity of reports of MI in living first degree relatives was 72% (58/81). The positive predictive value of such reports was 64% (58/90). For deceased relatives reported as dying of MI the sensitivity was 66% (121/183) and the positive predictive value was 76% (121/159). There were no differences in these proportions between cases and controls. The overall kappa scores were modest, 0.73 for cases and 0.65 for controls.

Whereas the odds ratio (OR) for a reported history of MI in at least 1 parent was 1.58 (95% Confidence Intervals (CI), 1.02 to 2.45), the OR for a validated history of MI in at least 1 parent was 1.64 (95% CI, 1.05 to 2.54). However, the OR for a reported history of MI among siblings was 1.75 (95% CI, 1.02 to 2.94), slightly greater than the OR for a validated history of MI in these kin (1.59; 95% CI, 0.93 to 2.72).

These results suggest that there may be some recall bias affecting self-reported family histories of MI among siblings in this Belfast ECTIM sample. The relatively modest sensitivity and positive predictive value may limit the overall effectiveness of a targeted screening programme for risk factors for myocardial infarction

THE IMPACT OF APOLIPOPROTEIN E POLYMORPHISM ON LIPOPROTEINS AND RISK OF MYOCARDIAL INFARCTION; THE ECTIM STUDY

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In the ECTIM Study, 574 male patients aged 25-64 years were examined 3-9 months after myocardial infarction in 4 regions participating in the WHO-MONICA Project. Controls (n=722) were randomly selected from the background population. Results were adjusted for age, centre, body mass index and alcohol consumption reported using a standardized questionnaire. The distribution of Apo E phenotype was significantly different across the 4 control samples ($p=0.04$) with a higher frequency of epsilon 4 allele in Belfast than Toulouse. The association of Apo E polymorphism with biological measurements was studied in the control groups (n=644). Allelic effects were estimated from a codominant genetic model. Individuals carrying the epsilon 2 allele had lower levels of plasma chol, LDL-chol and Apo B. TG, VLDL-chol, Apo CIII, Apo E, LpCIII:B and LpE:B levels were higher. The epsilon 4 allele was associated with increased Apo B level and decreased LpAI level. Subjects with the epsilon 4 allele had higher TG, VLDL-chol, LpCIII:B levels than those having the Apo E3/3 phenotype. Relative risk (RR) for MI associated with Apo E phenotypes in comparison with Apo E3/3 were found to increase in the following order: E2/2<E3/2<E3/3(RR=1)<E4/3=E4/2<E4/4($p<0.05$). The presence of the epsilon 2 and epsilon 4 alleles carried a respective relative risk of 0.73 ($p=0.05$) and 1.33 ($p=0.02$) in a codominant model logistic model. In conclusion, Apo E polymorphisms explain a modest proportion of myocardial infarction in the ECTIM Study.

APOLIPOPROTEIN B POLYMORPHISMS IN THE ECTIM STUDY

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The aim of the ECTIM study is to identify genetic factors involved in the development of myocardial infarction (MI). More than 600 patients with MI and 700 controls were recruited from 4 populations, in France (Lille, Strasbourg, Toulouse) and Northern Ireland (Belfast). Several lipid variables including LDL-cholesterol, Apo B and polymorphisms of the Apo B gene including the EcoRI, MspI, XbaI, signal peptide (SIPE) and 3'HVR were investigated in all participants.

Homozygotes and heterozygotes for the 48 repeats allele (HVR48+) were more frequent in cases (21.8%) than in controls (15.0%) ($p<0.003$ after adjustment on population). No statistically significant heterogeneity of this association could be detected across populations. The population adjusted odds-ratio (95% confidence interval) for MI was 1.55 (1.15-2.07) and the fraction of cases attributable to the HVR48+ genotype was 0.074. Body mass index (BMI) was positively associated with MI in HVR48+ individuals ($p<0.004$) but not in HVR48- individuals. In HVR48+ individuals, the mean excess weight (standardized to a height of 1.75 m) in cases relative to controls was: 6.6 kg in Belfast, 6.3 kg in Lille, 2.5 kg in Strasbourg and 2.3 kg in Toulouse. In individuals with a BMI>26 kg/m^2 (the median of BMI in controls), the population adjusted odds-ratio for MI associated with the HVR48+ genotype was 2.21 (1.47-3.31) ($p<0.0001$) and the fraction of cases attributable to the HVR48+ genotype was 0.14. In contrast, in individuals with a BMI<=26 kg/m2, the HVR48+ genotype was unrelated to MI.

In Belfast, in addition to the HVR48 polymorphism the SIPE polymorphism was also associated with MI. Significant associations were also observed between the Apo B signal peptide polymorphism and mean levels of total cholesterol, LDL cholesterol, ApoB and Lp(a) in the Strasbourg control population. Individuals homozygous for the rare allele had higher levels of these lipid parameters. In Belfast, although not statistically significant, the Apo B signal peptide polymorphism had a similar effect on Apo-B-related parameters as seen in Strasbourg. No significant associations were observed in the Toulouse population where the risk of MI is three times lower than in Belfast.

Finally, the polymorphisms investigated in the ECTIM study were in strong linkage disequilibrium and these disequilibria were of similar magnitude in the four populations. These last results suggest that in the presence of one of several variants of the Apo B gene carried by the HVR48 allele, overweight has a deleterious impact on lipid metabolism and raises the risk of MI.

(CA)n REPEAT POLYMORPHISM OF THE APOLIPOPROTEIN AII GENE: RESEARCH OF ASSOCIATION WITH MYOCARDIAL INFARCTION AND LIPOPROTEIN LEVELS: THE ECTIM STUDY

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Apolipoprotein AII (ApoAII) is the second major High Density Lipoprotein (HDL) component with apolipoprotein AI. In a multicentre retrospective study of myocardial infarction, the ECTIM study, we explored the association of an ApoAII gene polymorphism with coronary heart disease and with lipid and lipoprotein plasma levels. We studied a (CA)n repeat length polymorphism located in intron 2 of the gene. The ECTIM study was carried out in four regions: Belfast area, Toulouse area, Strasbourg area and Lille area. A sample of men aged between 25 and 64 was recruited: cases of myocardial infarction were included and controls were selected from the general population as age matched controls for myocardial infarction cases. The (CA)n repeat genotypes were detected with PCR amplification technique in 1358 subjects (595 cases and 763 controls). We identified 10 different alleles. The effect of this polymorphism on lipids and lipoproteins was analysed in the control group for subjects without any hypolipidaemic drugs.

	22	2X	XX	p
ApoAII(mg/dl)	33 (8)	35 (8)	37 (8)	0.0001
HDL Chol.(mg/dl)	52 (15)	51(15)	52 (15)	NS
LDL Chol. (mg/dl)	146 (33)	150 (39)	159 (42)	0.007

Allele 2 thus appeared to be associated with ApoAII plasma levels and influenced the levels of LDL-Cholesterol plasma levels, but not HDL-Cholesterol plasma levels. However, no association of this allele 2 with the disease was observed.

(TTA)n REPEAT POLYMORPHISM OF THE HMG CoA REDUCTASE GENE: RESEARCH OF ASSOCIATION WITH MYOCARDIAL INFARCTION AND LIPOPROTEIN LEVELS: THE ECTIM STUDY

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HMG CoA reductase is a key enzyme in the initial steps of cholesterol metabolism. Regulation of the rate of cholesterol biosynthesis is, in general, mediated by regulation of HMG CoA reductase activity. In a multicentre retrospective study of myocardial infarction, The ECTIM study, we explored the association of a HMG CoA reductase gene polymorphism with coronary heart disease and with lipid and lipoprotein plasma levels. We studied a (TTA)n repeat length polymorphism located 10 kbp 3' of exon 2 of the gene. The ECTIM study was carried out between 1988 and 1992 in four regions: Belfast (Northern Ireland), Toulouse (South of France), Strasbourg (North-East of France) and Lille (North of France). A sample of men aged between 25 and 64 was recruited: cases of myocardial infarction were included and controls were selected from the general population as age matched controls for myocardial infarction cases. The (TTA)n repeat genotypes were detected with PCR amplification technique in 1297 subjects (558 cases and 739 controls). We identified eight different alleles ranging from 10 to 17 repeats. The presence of at least one 15 repeat allele was significantly less frequent ($p<0.008$) in cases (14.7%) than in controls (20.4%). The effect of this polymorphism on lipid and lipoprotein levels was analysed in the control group for subjects without any hypolipidaemic drugs. The presence of at least one 15 repeat allele was associated with high levels of low density lipoprotein cholesterol ($p<0.003$). HMG CoA reductase gene polymorphism thus appears to be associated with the atherosclerotic process and coronary heart disease.

LIPOPROTEIN LIPASE GENE POLYMORPHISMS: ASSOCIATIONS WITH MYOCARDIAL INFARCTION AND LIPOPROTEIN LEVELS IN THE ECTIM STUDY

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Lipoprotein lipase (LPL) is a major determinant of the hydrolysis of triglyceride rich lipoproteins. Four DNA polymorphisms of the LPL gene were examined (PvuII, HindIII, Asn291 —>Ser and Ser447—>stop) to detect associations with lipid and lipoprotein levels and with the occurrence of myocardial infarction in the ECTIM study.

Significant pairwise linkage disequilibria were found between PvuII, HindIII and Ser447—>stop polymorphisms. Asn291—>Ser was in linkage disequilibrium with PvuII only.

Lipid related variables were analysed in the control group to avoid the bias resulting from lifestyle (treatment) changes after myocardial infarction. HindIII polymorphism was associated with apolipoprotein (Apo) C-III levels ($p=0.04$). Triglyceride, Apo B, Apo CIII and LpE-B levels were weakly associated with PvuII polymorphism ($0.05 < p < 0.10$). Ser447—>stop polymorphism was associated with triglyceride and Apo C-III levels ($p=0.04$ and $p=0.02$ respectively). No association between Asn291—>Ser polymorphism and lipid related variables was detected.

HindIII and PvuII polymorphisms were significantly associated with the occurrence of myocardial infarction, independently from their effects on triglycerides ($p=0.015$ and $p=0.006$ respectively, after adjustment on centre and triglyceride levels by multiple logistic regression). The relative risk of myocardial infarction (estimated by the odds ratio) for H2H2 subjects was 1.8 when compared to H1H1 (homozygotes for HindIII polymorphism). The relative risk for P2P2 was 1.4 when compared to P1P1 subjects (homozygotes for PvuII polymorphism). Moreover there was an interaction effect between PvuII polymorphism and triglyceride levels on myocardial infarction: triglycerides were associated with myocardial infarction only in P1P1 group ($p=0.006$).

These results indicate an effect of the genetic variation(s) of LPL on myocardial infarction. This could be due to the central role of LPL in lipoprotein metabolism, including the post-prandial phase, and not only to an effect on fasting lipoproteins.

GENETIC VARIATION AT THE B FIBRINOGEN LOCUS IN RELATION TO PLASMA FIBRINOGEN CONCENTRATIONS AND RISK OF MYOCARDIAL INFARCTION

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Increased plasma fibrinogen concentration is a major cardiovascular risk factor. Conflicting results on genetic variations in plasma fibrinogen levels have been reported. Furthermore, whether fibrinogen genotype is associated with the risk of ischaemic heart disease has not been studied so far. An HaeIII restriction fragment length polymorphism (RFLP) of the ß-fibrinogen gene was used in a case-control study to investigate the genetic variation at this locus in relation to plasma fibrinogen concentrations and the risk of myocardial infarction (MI). Five hundred and thirty-three male patients and 648 control subjects were recruited from 4 WHO MONICA centres in Northern Ireland and in France. The absence of HaeIII cutting site (H2 allele) was associated with a significant rise in fibrinogen concentrations in both patients and controls. The effect of the HaeIII polymorphism on plasma fibrinogen levels did not significantly differ between centres. Fibrinogen levels were higher in smokers than in non-smokers. The difference between the two groups was larger in subjects with the genotype H2H2 than in those with the genotype H1H1 or H1H2, regardless of the case-control status. However, there was no significant interaction between smoking status and genotype in its effects on fibrinogen levels. HaeIII genotype accounted for about 1% of the total variance in fibrinogen levels, whereas smoking and age together explained 7% and 5% in controls and patients, respectively. The frequency of the H2 allele was 0.21 in controls and 0.19 in patients. The estimate of relative risk for MI associated with the presence of the H2 allele was 0.89 (95% confidence interval: 0.69 - 1.13). The results were consistent with respect to the centres. Multiple regression analysis showed that smoking and raised plasma fibrinogen made independent contributions to the increase in MI risk. There was no significant interaction between HaeIII genotype and the effect of smoking on MI risk. These data provide further evidence for a role of the genetic variation at the ß-fibrinogen locus in the determination of plasma fibrinogen concentrations. However, this study failed to detect an association between this genetic variation and the MI risk. Further investigations are needed to assess the relative contribution of genetic and environmental determinants of plasma fibrinogen to the prediction of atherothrombotic diseases.

FACTOR VII GENOTYPE DETERMINES FACTOR VII COAGULANT ACTIVITY IN THE ECTIM STUDY

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Raised plasma level of factor VII coagulant activity (fVIIc) has been implicated as a risk factor for myocardial infarction (MI) and so genetic factors determining an individual's fVIIc level may influence risk of MI. We have, therefore, genotyped individuals taking part in the ECTIM study for the Arg/Gln$_{353}$ polymorphism of the factor VII gene. This polymorphism has previously been shown to be strongly associated with plasma fVIIc. This was confirmed in the ECTIM study, where the Gln allele was associated with significantly lower fVIIc levels in both MI cases and controls in all centres, with the exception of Lille controls where a similar but non-significant trend was observed. Among the MI cases, the mean fVIIc level in the Arg/Arg homozygotes was 115% of standard, in the heterozygotes was 102% and in the Gln/Gln homozygotes was 78%, with $p<0.0001$ (by ANOVA). The corresponding values for the controls (excluding those on oral anticoagulants (OACs) and those with coronary heart disease (CHD)) were, respectively, 118%, 104% and 91%, with $p<0.0001$. The frequency of the Gln allele did not differ significantly between centres or between cases and controls, with the frequency in the controls (excluding CHDs and those on OACs) being 0.12 (95% CI 0.10-0.14) and in the MI cases being 0.11 (0.08-0.12). This suggests that the factor VII Arg/Gln$_{353}$ polymorphism may not be a strong determinant of risk of MI despite its effect on fVIIc levels. A previous study had suggested that the correlation of plasma fVIIc and triglyceride levels may be stronger in Arg/Arg homozygotes than in Gln allele carriers, however, this was not confirmed in the ECTIM study, with the possible exception of the Belfast sample which showed a similar trend.

ASSOCIATION BETWEEN VARIATION IN THE PROMOTER REGION OF THE PLASMINOGEN ACTIVATOR INHIBITOR-1 (PAI-1) GENE AND PLASMA PA1-1 ACTIVITY: THE ECTIM STUDY

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We have studied the association of a common insertion/deletion polymorphism in the plasminogen activator inhibitor-1 (PAI-1) gene promoter with plasma levels of PAI-1 activity in 474 patients with myocardial infarction and 638 matched controls from the four centres participating in the ECTIM study. In the Belfast samples PAI-1 levels were higher in patients than controls (8.0% $p<0.05$), while in the three French centres levels were higher in the controls than in the patients. The frequency of the deletion allele (4G) was similar in patients and controls (0.57 and 0.55 respectively) and it was associated with elevated levels of plasma PAI-1 in both groups. The effect of genotype on PAI-1 levels was consistent in all regions and was greater in patients than controls, but was statistically significant only in the patients from Belfast and Strasbourg and in the patient sample as a whole ($p<0.05$). After adjusting for differences between centres, body mass index and plasma triglycerides, which affect levels of PAI-1, patients and controls homozygous for the 4G allele had mean PAI-1 activities, respectively, 17.6% and 6.5% higher than 5G homozygotes, with heterozygotes having intermediate values. In both patients and controls from Belfast there was a positive correlation between plasma fibrinogen levels and PAI-1 activities in 4G homozygotes ($r=0.23$ $p=0.06$, $r=0.24$ $p=0.08$ respectively), while in those with other genotypes this correlation was negative. This relationship was observed only weakly in the patients and controls from the French centres. These data are consistent with a previous study showing a differential effect of cytokines on transcription from the two alleles in HepG2 cells, and confirm that variation at the PAI-1 locus contributes to inter-individual differences in plasma PAI-1 levels, especially during the acute phase. This suggests that this polymorphism may be one of the genetic factors that determines an individual's risk of thrombotic disease.

ACE INSERTION/DELETION POLYMORPHISM: A NEW RISK FACTOR FOR MYOCARDIAL INFARCTION?

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About 25% of the variability of plasma ACE level is associated with an Insertion (I)/Deletion (D) polymorphism of the ACE gene which is a marker for an unknown functional variant situated within or close to the ACE gene. As a chronic exposure to high ACE levels may modulate the activity of peptides involved in vasoconstriction and smooth muscle cell proliferation and predispose to myocardial infarction (MI), we considered that the ACE gene could be a candidate for MI. To test this possibility, the frequency of the ACE I/D genotypes was compared in patients with MI (n=610) and controls (n=733) participating in the ECTIM study in Belfast, Lille, Strasbourg and Toulouse. The DD genotype was more frequent in patients than in controls, especially in those considered to be at low risk (plasma Apo B<1.25 g/l and BMI<26 kg/m^2). In this subgroup which represented 13% of the patients, the relative risk of MI associated with the DD genotype was approximately 3 and the attributable risk was 30%. In control subjects, parental history of fatal MI was associated with a significantly higher frequency of the D allele in Belfast as well as in France. These results which will have to be confirmed in other studies and other populations suggest that the ACE/ID polymorphism is a new potent risk factor for MI.

ECTIM AND FUTURE STUDIES IN BELFAST

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Some caution is appropriate before the results from ECTIM to date are more widely generalised. Ongoing MONICA registration and the ECTIM Family study in Belfast may allow some of this reservation to be addressed in extensions of the protocol.

i In particular, ECTIM cases were recruited within nine months of *surviving* a myocardial infarction. The fact that some alleles (such as the ACE insertion/deletion polymorphism) seem to confer greater risk to surviving patients with an otherwise low risk profile suggests that these alleles may be implicated in *fatal* MI in patients with other established risk factors. It is thus intended that post-mortem tissue from subjects dying early in the course of MI is retrieved (n=200), DNA recovered from the archived material and the frequency of "susceptibility" genotypes determined.

ii Although the incidence of ischaemic heart disease in men is substantially greater than in women, coronary heart disease is one of the most common causes of death in both sexes. Though there is epidemiological evidence indicating a gradient of risk to women from "traditional" risk factors such as smoking, hypertension or raised serum cholesterol, the attributable risks are often found to be somewhat smaller than in men. The Belfast ECTIM extension will recruit 200 female cases and 200 female controls. This will allow a comparison with the findings in Belfast men on the importance of the lipoparticle profiles and specific genetic determinants of risk. This may point to the need for further studies in other centres.

iii A natural extension of the study of population associations between genotypes and disease is to discover whether the "susceptibility" alleles segregate with the disease (or trait) in specific families. The validated family history data on Belfast ECTIM subjects will allow ready identification and recruitment of at-risk families for linkage and, eventually, intervention studies.

BELFAST HYPERLIPIDAEMIA STUDY

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It is well established that when LDL receptors are deficient, LDL cholesterol accumulates and coronary risk is greatly increased. Similarly, it is known that certain variants of apolipoprotein B 100 (eg when there is a mutation in the codon for the amino acid 3500) result in poor binding between the apolipoprotein and the LDL receptor with cholesteryl ester-enriched LDL particles consequently accumulating in the plasma. The 3500 polymorphism was rare in the ECTIM Study. The Belfast Hyperlipidaemia Study will investigate those types of Frederickson hyperlipoproteinaemias which are associated with increased levels of apolipoprotein B 100, mainly (Type IIA, IIB and IV) in relation to several polymorphisms of the apolipoprotein B gene. Two hundred previously untreated patients will be recruited from the lipid clinic of the Royal Victoria Hospital, Belfast. Male patients aged 40-64 years and female patients aged 50-64 years will be eligible. All should have types IIA, IIB or IV hyperlipoproteinaemia and both of their parents should have been born in the historical entity of Ulster. Twenty mls of blood will be drawn at EDTA after a full overnight fast. Polymorphisms of the apolipoprotein B gene of special interest are (1) variants already published: Apo B/XbaI, EcoRI, signal peptide, 3500, 4311 biallelic polymorphism; Apo B 3'HVR (2) new variants of the apolipoprotein B gene identified in the ECTIM Study and (3) other polymorphisms. Biochemical estimations will be carried out in the Department of Medicine, The Queen's University of Belfast and the apolipoprotein B and other polymorphisms are to be investigated at INSERM SC7, Paris. It is estimated that the study will take 18 months – 2 years to complete.

THE PRIME STUDY

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The PRIME Study is a prospective study of the determinants of coronary heart disease incidence and mortality in 50-59 year old males in the MONICA Centres in France and Northern Ireland. The Study is building on the findings of the ECTIM Study. The four centres provide a stark contrast in ischaemic heart disease incidence with rates in Belfast four times those in Toulouse and more than three times those in Lille and Strasbourg. Subjects are drawn from General Practice, Health Check-up Centres and Industry in the four centres and are screened after a full overnight fast. Total intake to the study will be close to 11,000 and already approximately 8,500 subjects have been recruited. Screening began in mid 1991 and will be completed later this year and thereafter 5-7 year follow-up will take place. The high-risk lipid profile, i.e. low LPA1 and high LPE:B and LP(a) observed in Belfast will receive special attention and these factors will be measured in fresh plasma from each subject. The environmental factors of special interest are diet (in particular fatty acids and the major antioxidant vitamins A, E and C). Alcohol consumption with special reference to type of beverage and amount and pattern of drinking, physical activity, cigarette consumption, drug intake, psychosocial factors including shift work and family histories are also being investigated. Gene environment interactions are of key interest, especially in relation to polymorphisms of the apolipoprotein B gene and the DD polymorphism of the ACE gene. The study will also look at other lipid parameters, thrombotic factors and hormones.

POSTSCRIPT

After the meeting Dr Pierre Ducimetière unveiled a plaque at 7 Marcus Square, Newry to commemorate Dr Samuel Black, the pioneer Cardiologist who lived there from 1819 - 1832. Dr Black was first to notice the large disparity in heart disease between the north of Ireland and France. The plaque was erected by the Ulster History Circle with the generous assistance of Newry and Mourne District Council.

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